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and Medical News

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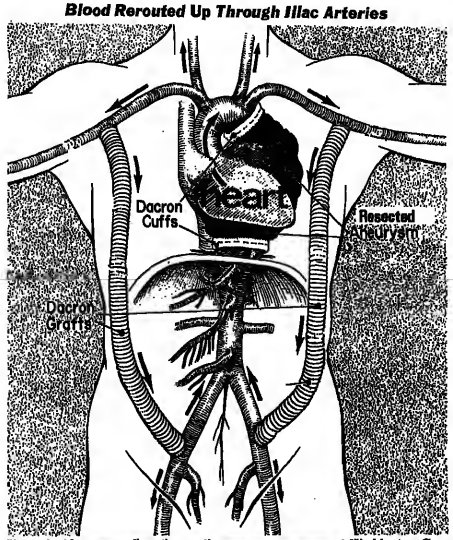
making rounds at press time

PACKAGE INSERTS – FDA will formally propose new guidelines for prescription drug package inserts "in the next few weeks," Dr. Vincent Gagliardi of the Bureau of Drugs told MT. Especially emphasized will be new sections on pregnancy, labor and delivery, and nursing mothers. Stronger warnings are needed in these areas, according to Dr. J. Richard Crout, head of the Bureau of Drugs, due to "great societal neglect" of drug misuse in obstetrics.

THE LOWLY COCKROACH – will be studied at the Sloan-Kettering Research Center to determine if and why invertebrates are resistant to cancer. Project director Robert S. Anderson, Ph.D., told MT he thinks roaches and other species low on the phylogenetic scale "may synthesize some substance that blocks the action of carcinogens."

BREAST ENLARGMENTS, face lifts, and 631 other plastic surgery procedures at Portsmouth Naval Hosp. were billed to taxpayers last year, according to Rear Adm Harry Mahin, hospital commander. "In addition to the benefit to the women," he said in a statement, "plastic surgeons need to keep their talents sharp." Spokesman for Rep. Les Aspin commented, "In other words, they don't have anything else to do, so they do it for 'morale' purposes."

Blood Rerouted Up Through Iliac Arteries



To deal with a severe dissecting aortic aneurysm, surgeons at Washington General Hosp. connected subclavian and iliac arteries via Dacron grafts inserted bilaterally just outside the patient's rib cage, clamping off both ends of the aneurysm. The grafts reroute blood up through iliac arteries to organs of abdomen. The aneurysm was then excised.

Position Shift Effective

'Roll-Over' Test Flags High BP Of Pregnancy

By Ben Rose
Medical Tribune World Service

WINNIPEG, MAN. — Blood pressure readings in the lateral and supine positions are a highly effective way of screening patients for pregnancy-induced hypertension and its complications, it was reported here at the annual meeting of the Royal College of Physicians and Surgeons of Canada.

At the same time it was recommended by Dr. Norman Gant, Associate Professor and co-chairman of Obstetrics and Gynecology, University of Texas, Southwestern Medical Center, Dallas, that all women—young and old—in the highest risk group, primigravidas, should be given such a screening test.

In their experience, Dr. Gant said, the readings have proven 90 per cent accurate in predicting the development of pregnancy-induced hypertension 10 weeks later.

The test—referred to as the "roll over" technique—requires about 15 minutes to establish a base-line reading in the lateral position before the blood pressure is taken in the supine position.

"Not too many doctors want to *Continued on page 13*

Aneurysm Bypass Reverses Abdominal Aorta Blood Flow

By Ralph Cosham
Special Tribune Correspondent

WASHINGTON—Surgeons at the Washington Hospital Center have successfully bypassed a severe dissecting aortic aneurysm by means of axillary Dacron iliac grafts that have reversed the direction of the blood flow in the patient's abdominal aorta. The patient, a 54-year-old local government employee, is back at work and progressing well, according to Dr. Karel Absolon, chief of surgery at Washington Hospital Center.

The procedure was developed hemo- *Continued on page 12*

Pasteur Institute In Grave Plight; May Quit Paris

Famed Pasteur Institute attracts post-graduate students from all nations, but financial problems place its future in question. See pages 14 and 18.

For Most Serious Infections Only . . .

Warning Issued on Clindamycin, Lincomycin

By Alan Fitzgibbon
Special Tribune Correspondent

WASHINGTON—Clindamycin and lincomycin, two widely prescribed antibiotics, may produce hazardous side effects and should not be prescribed for any but the most serious infections, an expert coosultative panel of the Food and Drug Administration has warned.

The possible dangers of the two drugs have been widely publicized since mid-January, when the director of the consumer-oriented Health Research Group here wrote the Commissioner of the Food and Drug Administration that "more than 15" deaths from bloody colitis has occurred following use of clindamycin and that "well over 75 per cent" of clindamycin prescriptions were written to treat minor ailments for which neither it nor lincomycin should be prescribed.

After hearing reports for and against the two antibiotics at its most recent meeting, the F.D.A.'s nine-member Anti-Infective Agents Advisory Committee concluded that available data do not warrant the removal of the drugs from the market.

But it recommended that the F.D.A. strengthen warnings in the labeling and package inserts that accompany the two antibiotics. In addition to noting that their use may produce colitis, as is now done, the labeling should limit use of the drugs to severe infections against which less toxic antibiotics are *Continued on page 2*

Warning Issued on Clindamycin, Lincomycin

Continued from page 1

unavailing and should contain a warning that death may occur, the panel said.

The F.D.A. should also send a letter to all physicians pointing out the dangers of clindamycin and lincomycin and warning against their over-prescription, the panel recommended. The agency has indicated that it will follow the advisory committee's suggestions.

In his January 16 letter which touched off the storm over the two antibiotics, Dr. Sidney Wolfe, director of the Health Research Group, said that the Upjohn Company, which makes the agents, "has continued to promote this drug [clindamycin] for treating upper respiratory infections. As a consequence, the treatment of minor infections and use for prophylaxis makes up well over 75 per cent of the use of the drug." Of the estimated 6,000,000 prescriptions written in 1973 for clindamycin, 4,525,000 were for colds, sore throats, other acute upper respiratory infections, sinusitis, acne, middle ear infections, or surgical aftercare, he said.

Would Limit Use to Inpatients

Because of what he called the considerable incidence of sometimes fatal side effects produced by clindamycin and lincomycin, Dr. Wolfe urged the F.D.A. to restrict the agents' use to hospitalized patients with "appropriate infections."

Shortly after receiving Dr. Wolfe's letter, the F.D.A. issued a statement saying its files showed there had been 15 deaths—nine associated with clindamycin and five with lincomycin—from October 1969 through June 1974. The deaths were among patients of all ages, but some were elderly or seriously ill from other conditions such as cancer or heart disease and had undergone major surgery, the F.D.A. said. It noted that during the same period more than 200 cases of colitis associated with the drugs had been reported to it, and that in August 1974 it had included a warning about colitis as a possible side effect in their labeling.

An Upjohn spokesman responded to Dr. Wolfe's charges by saying that the company promoted clindamycin and lincomycin only for the uses approved by the F.D.A. He noted that a clindamycin study revealing a 10 per cent incidence of colitis which Dr. W[...] had cited covered only 200 p[...] and that other studies of clini[...] use showed no resulting colitis.

Upjohn has marketed lincomy[cin] Lincocin since 1965 and clinda[mycin] as Cleocin since 1970. Industry [...] estimate annual sales of the che[...] related agents at $170,000,00[0] about 20 per cent of the com[...] worldwide revenue, but estima[...] the annual number of prescrip[...] written for them vary from 7,00[...] for both to Dr. Wolfe's 6,000,00[0] each.

At the same time the F.D.A [...]visory committee was meeting[...] Gaylord Nelson convened hi[...] nopoly subcommittee of the S[...] Small Business Committee fo[r] days of hearings on the drugs.

The Wisconsin Democrat's op[...] statement and the testimony of s[...] physicians about the agents' d[...] were largely a repetition of the m[...] Dr. Wolfe had cited in his lette[r] charges therein, or comment befo[re] advisory committee, but Dr. Alex[...] M. Schmidt, the F.D.A. Commis[sioner] did say that a new survey by his a[...] had revealed 32 deaths associated [with] the use of clindamycin or linco[mycin].

6 of 32 Previously Reported

Six of the 32 deaths had bee[n re]ported in the literature and the re[main]ing 26 had come to the F.D.A.'s [atten]tion through its adverse drug re[action] reporting system, most of them [...] recently. In many of the latter [...] colitis was considered a major or [con]tributory cause of death, and ma[ny of] the 32 patients who died were el[derly,] already had serious diseases other [than] possible colitis, and were taking [other] antibiotics. Twenty of the deaths [were] associated with clindamycin use [and] 12 with lincomycin use.

Dr. William N. Hubbard, Jr., [presi]dent of Upjohn, defended clinda[mycin] and lincomycin as valuable in tr[eating] certain types of infection, incl[uding] penicillin-resistant staphylococcu[s in]fections. He said that neither d[rug is] now being promoted, partly becau[se of] rapidly changing knowledge abo[ut the] usefulness and potential hazard[s of] each.

Old Contraceptives List Camel Foam—and Wor[se]

Medical Tribune World Servi[ce]

TORONTO—A list of "contrac[eptive] agents" from early days, includin[g ...]nic acid, lemon juice douche, [...] beans, parsley, opium, elephant [...] camel dung, willow, a piece of [...] tied in three knots, gunpowder [...] foam from a camel's mouth, and [...] ping three times over a grave [...] mentioned here in an lighter [...] an international conference on [Pre]scription Drugs and the Pu[blic] Health."

Dr. J. Fraser Mustard, [...] Faculty of Medicine, McMaster [Uni]versity, Hamilton, gave the lis[t ...] tracing development of oral contr[acep]tives.

"Some of these, including the [lemon] juice douche, were probably partl[y ef]fective," he said, adding: "N[...] equalled the suggestion in the Me[dical and] Surgical Reporter in 1888 by a [...] Pearce, who wrote: 'Before go[ing to] bed, drink a glass of cold water [and] don't touch another thing.'"

Health Budget Reflects Fund-Cutting Policy

Medical Tribune Report

WASHINGTON—President Ford has asked Congress to authorize $4.5 billion for the government's health activities other than Medicaid and Medicare in fiscal 1976.

The budget he has proposed for the agencies of the Public Health Service and the office of the Assistant Secretary for Health in the Department of Health, Education, and Welfare represents an increase of only 0.2 per cent over the revised fiscal 1975 budget and is in line with the President's policy of cutting government expenditures to deal with the country's economic problems.

If inflationary erosion is taken into account, the fiscal 1976 health budget would represent a decrease in real spending money. Only the Health Resources Administration and the Assistant Secretary's office would have more funds available for their programs after next July 1 than during the present fiscal year.

Federal accounting practices are almost totally unlike those of the average family and only remotely like those of the average business.

How Budget-Making Works

After months of preparation, the President submits to Congress sometime during January or February his proposed budget for the coming fiscal year, which starts on the following July 1 and is named after the next year. Specialized appropriations subcommittees of the two houses of Congress then consider budget proposals for the various executive departments, often revising them upward or downward. When they and their parent appropriations committees have had their final say, the Senate and House must jointly vote an authorization, or ceiling on the amount any department may spend during the coming fiscal year. If Congress does not approve an authorization by July 1, as often it does not, it generally votes to let a department keep going at its current funding level under a continuing resolution.

Once it has authorized a budget, Congress must appropriate the money for it. Frequently it does this late in the fiscal year for which the budget has been authorized, and sometimes in the appropriation process it further changes an Administration's initial proposals or its own earlier authorization.

'Washington Shell Game'

As budget-making progresses after each February, the Administration, too, is free to change its proposals. In what has sometimes been called the "Washington shell game," Administrations often ask for high budgets in February for political reasons and revise their requests downward later in the year for financial ones.

During the Nixon years the Administration impounded Congressionally authorized and appropriated funds it did not want to spend, but the Nixon impoundments were without Congress's approval and were generally overturned by the courts. The Ford Administration's term for the now unpopular "impoundment" is "rescission," and under a recently enacted law Congress must approve rescission requests. Since many government programs statutorily last for more than one year and Congress initially authorizes annual budgets for each of their years, rescissions may be requested for previously authorized funds in addition to those proposed for the coming fiscal year.

President's Ford's proposed fiscal 1976 health budget, which includes $516,000,000 in proposed rescissions from previous appropriations, calls for possible spending of $4,546,000,000, an increase of $7,000,000 or 0.2 per cent over his revised fiscal 1975 budget.

The agencies due for the largest changes in their budgets are the Health Services Administration, for which a cut of 13.1 per cent has been proposed, and the Health Resources Administration and the office of the Assistant Secretary for Health, for which the Administration has requested budget increases of 20.4 and 11.3 per cent, respectively.

Less money is being asked for HSA next year because the Administration wants state and local governments as well as third-party reimbursers—all of which it feels are financially better off than the federal government—to pay for and run many of the services the agency has so far performed. Budget cuts have been proposed in four of HSA's largest programs, $67,000,000 in the comprehensive health formula grants program, $41,000,000 in the community health centers program, $53,000,000 in the maternal and child health program, and $21,000,000 in family planning services.

	1975 Revised (In Millions)	1976 (In Millions)	Change from 1975 (%)
Food and Drug Administration	$ 201	$ 203	+ 1.0
Center for Disease Control	140	133	− 5.0
Health Services Administration	1,160	1,008	−13.1
National Institutes of Health	1,733	1,805	+ 4.2
Alcohol, Drug Abuse, and Mental Health Administration	723	702	− 2.9
Health Resources Administration	520	626	+20.4
Assistant Secretary for Health	62	69	+11.3
Total	4,539	4,546	+ 0.2

National Institutes of Health	1975 Revised (In Millions)	1976 (In Millions)	Change from 1975 (%)
Cancer	$ 569	605	+ 6.3
Heart and Lung	286	293	+ 2.4
Dental	42	44	+ 3.7
Arthritis	145	148	+ 2.6
Neurology	112	115	+ 2.7
Allergy	105	109	+ 3.1
General Medical Sciences	157	162	+ 3.2
Child Health	118	106	−10.1
Aging	—	16	—
Eye	38	39	+ 4.2
Environmental Health	28	31	+11.0
Research Resources	81	81	+ 0.5
Fogarty International Center	5	5	+ 0.4

Note: Percentage changes above are based on thousand-dollar amounts.

Much of the increase proposed for the Health Resources Administration budget would finance its new health planning program, and the increase proposed for the Assistant Secretary's office reflects a continuing trend toward the centralization of health policy-making therein with its consequent increased need for staff.

The Inflation Factor

Since government budget makers work with constant dollars, there is a certain degree of unreality in the health and other budget proposals the administration has presented to Congress. Inflation affects various government programs differently because among other reasons, equipment-intensive programs tend to suffer from it more than those which do not require expensive research apparatus, and many administrators candidly say that while they know inflation will hurt their work, they do not know how badly. Those willing to make guesses put the inflation factor affecting their programs at between 6 and 10 per cent. —A.F.

ECTOPIC BEAT

The language gets very strange, we judge after reading a release from the Southern Medical Associatino that said: "The Southern Medical Association Cancer Information Center has been refunded for a two-year period. . . ."

[Regular feature: Immateria Medica, page 23.]

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CLINICAL NEWS NOTE: *"Our system suffers from inability to validate clinical experience of the more usual type—the experience of the clinician weighs so little in the scale. Physicians, to be sure, are not always right, but they are not always wrong. We should be able to use their clinical experience better than we are now doing." (Dr. Louis Lasagna, see pg. 18.)*

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Medical Tribune

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Current Opinion

Adverse Drug Reaction in the United States

BY DANA L. FARNSWORTH, M.D.

Chairman, Board of Directors, Medicine in the Public Interest; Henry K. Oliver, Professor of Hygiene Emeritus, Harvard University; Consultant on Psychiatry, Harvard School of Public Health, Boston.

This is the first of a series of reporting on an objective analysis of adverse drug reactions by leading specialists. The study was sponsored out by the Medicine in the Public Interest (MIPI) which has its purpose the "conducting of studies, performing analysis and making evaluations of present policies that the government cannot or will not perform and to do so in an objective fashion . . . so that policymakers and the public will be informed . . ." Full copies of the Report are available at $1.50 each from MIPI, Suite 720, 600 New Hampshire Ave., NW, Washington, D.C. 20037.

As the medical profession and patients have become increasingly dependent upon drugs, more and more concern continues to be expressed about their misuse and abuse. Recent reports that thousands of Americans are harmed or suffer fatalities from the side effects of modern medications, publicized most notably by recent hearings of Senator Edward M. Kennedy's Senate Health Subcommittee, have made objective studies of such rumors necessary. Such *estimates* of unnecessary deaths each year, resulting from medications in hospitals alone, have soared to 120,000 to 140,000 yearly needed to be verified.

Medicine in the Public Interest, a non-profit organization devoted to investigation of questions in which Medicine, Law and Government have common concern, has sponsored a study of this question and obtained the best available authorities in the field to do the investigation. Its report, prepared by Drs. Louis Lasagna and Fred Karch of the University of Rochester School of Medicine and Dentistry, with the aid of six of the most knowledgeable consultants in the nation in the fields of pharmacology, statistics, and medicine has very recently been released.

"... the data base on which current estimates of the extent of the problem [adverse drug reactions] figured was completely unreliable. Many relatively minor reactions were classified with major ones."

Their study, *Adverse Drug Reactions in the United States,* did, in fact, show that the data base on which current estimates of the extent of the problem were figured was completely unreliable. Many relatively minor reactions were classified with major ones. Extrapolations of data from acute medical wards were often applied to all other services, resulting in statistics more alarming than accurate. Older standard drugs were found to be as dangerous, or even more so, than those newly developed.

A strong possibility exists that more patients are harmed by not taking drugs that are specifically indicated for their illnesses, than by drugs that are prescribed. No controlled studies have been done. Gloomy statements and predictions have added to public uneasiness and distrust, leading to the hope that such practices should be deferred until reliable data is developed.

The directors and members of MIPI hope that this study will stimulate the development of firmly based and adequate knowledge that will indeed promote more effective care for all persons.

Recognizing Role of Drugs

Among the radical improvements in easing human misery, the development of drugs of all kinds deserves a very high place. Ever since the demonstration of anesthesia to permit surgical operations without pain in the 1840s, the rate of progress has been constantly accelerating, but so have the unfortunate complications of misuse, either inadvertently or voluntarily. When tragedies occur people look for causes, and thus physicians and drug manufacturers often find themselves being criticized, sometimes properly, and sometimes not.

Since drugs can be powerful agents either for good or harm, their adverse effects are of prime interest to everyone, though with different intensity and significance depending on whether one is a recipient or an agent in developing and delivering them. In recent years criticisms, always desirable when indicated, have at times become regrettable when based on constantly changing and insufficient facts.

"The directors and members of Medicine in the Public Interest hope that this study will stimulate the development of firmly based and adequate knowledge that will promote more effective care for all persons."

The use of drugs will always be accompanied by some dangers, but the ideal goal is learning how to use them as safely as possible, keeping the risk factors low, and maintaining close supervision for early detection of idiosyncratic reactions. Under these circumstances their contribution to the relief of human suffering is incalculable.

As society has become more efficient in dealing with the woes of mankind it has at the same time become increasingly subject to criticism when those benefits are not equitably shared by all those who need them. Thus the medical profession and its allies in the health care system have become victims of their own successes, in the sense that they can do marvelous things to relieve pain and suffering but often only at a high monetary cost. The poor often cannot benefit from life-saving procedures that are inordinately expensive and may become disillusioned and bitter. Hence a central aim of all those who seek to relieve human suffering is, or should be, making all life-saving and pain-relieving procedures available to all who need them. The cooperation of many persons and professions are needed to achieve this ideal goal.

"The most important recommendations concerns the need for comprehensive studies that will enable reliable data to be obtained . . ."

The most important recommendation of the report concerns the need for developing comprehensive studies that will enable reliable data to be obtained regarding all types of adverse drug reactions. This will be a huge task, undoubtedly requiring federal as well as private funding over a considerable period. It will be expensive, but not as much so as not to do it, especially when measured in terms of human suffering.

Next week's Current Opinion will present highlights from the MIPI Study by Drs. Fred Karch and Louis Lasagna of the Department of Pharmacology and Toxicology of the University of Rochester School of Medicine and Dentistry.

House Calls by Rail Bike

Dr. Simno Morum, the only physician in Paranapiacaba, a small village in the state of São Paulo, Brazil, uses a "railway bicycle" to visit some of his patients. Dr. Maruoi, who is in his 70s, gave up a comfortable practice in a big city 30 years ago to go to Paranapiacaba. There is a major shortage of doctors in the interior of Brazil, and the goverment is now offering free housing and better salaries to attract physicians to the area.

Repeated Neurological Evaluation Of At-Risk Infants Held Necessary

Medical Tribune World Service

PRAGUE—The evolution of at-risk babies is "complicated and unexpected," and great caution should be exercised in making prognoses regarding their neurological development, Dr. Vladimir Vlach, of the Institute for Mother and Child, Prague, told the Fourth European Congress of Perinatal Medicine here.

In a population of such infants, he said, "new groups appear and disappear, normal newborns move from one group to another, the retarded emerge, and minor deviations are extinguished." The repeated neurological examination of at-risk children is therefore necessary, he said.

A study of 700 at-risk children from birth to 18 months found the following, Dr. Vlach related:

In the first week 52.8 per cent were diagnosed as normal, 4.1 per cent as retarded (these were premature), 35.3 per cent had slight neurological deficits, and 2.4 per cent serious deficits.

At three months the number of normal babies dipped sharply, but it rose again to 51.9 per cent at 18 months. A steeply rising trend was recorded by the retarded group, reaching 43.8 per cent at 18 months, while those with slight neurological deviations declined markedly to 2.7 per cent in the same period. Only the group with serious neurological findings remained almost constant, declining to 1.6 per cent chiefly as a result of four deaths in the first trimester.

Excluding Prematures ...

When prematures were excluded from the study, 59.7 per cent of the remaining neonates were assessed as normal. This figure dropped to 40.7 per cent at three months but rose to 47.6 per cent at 18 months. At three months, 27.4 per cent were retarded, but at 18 months the figure had risen to 48.7 per cent. Many of these had come from the group originally diagnosed as having slight neurological deficits. The latter comprised 38.6 per cent of the total at three months but only 2.6 per cent at 18 months.

When the prematures were judged separately, a different picture emerged. While 46.8 per cent were considered normal in the newborn period, 80.6 per cent had achieved normalcy at 18 months. The retarded prematures dropped from 33.7 per cent of the total in the first week to 11.8 per cent at three months, and remained at about that level thereafter—a trend diametrically opposed to that observed in the rest of the babies.

Co-authors were Drs. E. Ciperová and Jaroslava Zezuláková.

EDITORIAL CAPSULES

comments in current medical and scientific journals.

Needless Diagnostic Tests

"Unfortunately, most of these needless [diagnostic] tests originate in prestigious institutions connected with medical schools. Often they are performed on individual patients for 'academic reasons.' This is certainly a poor excuse for a needless test. Physician educators must strive to teach house staff and students clinical thoughtfulness and not how to squander money and time on needless and possibly dangerous tests. We should critically review all of our examinations. The ordinary white count can be dangerously misleading when called upon to rule out appendicitis, particularly in the emergency room. Simple contrast studies of the upper pouch in esophageal atresia seem harmless enough when performed by a skillful radiologist. However, we frequently see babies sent in from outlying hospitals whose lungs are flooded with contrast material. They are then at greater risk for pulmonary complications. A contrast study of the upper pouch is a lovely thing to show at conferences; however, we should teach our students that a simple P.A. and later film of the chest with a radiopaque catheter is all that is necessary. . . .

"These are only a few of the many unnecessary tests which are being recommended and performed in our teaching hospitals. Unfortunately, the idea soon gets around that not to perform a given test is close to malpractice. Consequently, outlying institutions feel compelled to overuse and rely on them unduly. New diagnostic tests should be subjected to the same vigorous evaluation as new drug therapy." (*Editorial, John G. Raffensperger, M. D., J. Ped. Surg. 9:807, Dec., 1974*)

Radionuclides Advantages

"The emergence in the past 20 years of nuclear medicine as a distinct diagnostic discipline has been a major clinical advance. . . . Application of these radionuclide techniques to the study of coronary artery disease has been quite recent . . . However, realization of the potential usefulness of these techniques has fostered an increasingly productive liaison between the two specialties.

"The potential advantages of these radionuclides in evaluating patients with cardiovascular disease is twofold: first they may permit the noninvasive or atraumatic acquisition of data that might otherwise be obtained only at the time of cardiac catherization, second, and perhaps more important, they may permit the acquisition of physiologic measurements or observations not attainable by more conventional modes of study. Functionally, these techniques can be divided into those that evaluate cardiac performance and those that evaluate coronary blood flow, regional myocardial perfusion and myocardial viability." (*Editorial, Barry L. Zaret, M. D., Lawrence S. Cohen, M. D., Amer. J. Cardiol. 35:112, Jan., 1975*)

Marmoset Ban Said to Hamper Virus Research

By James Magee
Medical Tribune World Service

Milan, Italy—A conservationist embargo on exports of marmosets from countries in South America is hampering research on hepatitis A and certain cancer tumor viruses, Dr. Frank T. Perkins, president of the International Association of Biological Standardization, warned here. The ban has come at a time when research progress has brought a vastly expanded need for the animals.

Until recently, the United States imported a few thousand a year. Now the supply has been cut off completely while the demand has jumped several fold.

World requirements for the animals now estimated at 50,000 annually, but early last year the countries of the Upper Colombia Basin—Brazil, Peru, and Colombia—banned all exports. Only a handful of laboratories in the United States are breeding them in captivity. The crunch has come during the past four or five months, and investigators at a viral hepatitis symposium of the International Association of Biological Standardization here made a plea for a supply of the small primates.

"As it is, the ban is serving neither conservation nor scientific research," said Dr. Perkins. "The animals are now being smuggled out of South America under such conditions that most of them are either dead or dying by the time they reach the black market in Europe, where dealers are offering them for about $100 per animal."

Breeding Called the Answer

Breeding marmosets is the only realistic answer to the problem, according to Dr. Friedrich Deinhardt, of the department of microbiology at Rush-Presbyterian-St. Luke's Medical Center in Chicago. "We saw this coming and have been trying to convince interested scientists to begin for the past 10 years."

The laboratory at Rush-Presbyterian began breeding marmosets in 1961 and now produces some 300 animals a year. But there are none to spare since the laboratory's own needs outstrip this supply.

"We started to use them for tumor virus research, but in insignificant numbers," Dr. Deinhardt told Medical Tribune. "The number needed increased considerably when it was shown that marmosets are susceptible to hepatitis A, in addition to six different tumor viruses, including one possible human tumor virus. They are also susceptible to slow viruses. And marmosets are really the only or the best model."

Earlier attempts to transmit hepatitis A or B to chimpanzees produced equivocal results, he noted, due to the fact that they often pick up hepatitis from man after capture, get a subclinical infection, and develop immunity before laboratory experiments can begin. In addition, they are costly to breed in captivity in comparison with marmosets.

Colon Polyps Are Removed During Fiberscope Studies

Medical Tribune World Service

MEXICO CITY—In 1,523 colonoscopic examinations with the fiberglass endoscope at the University of Erlangen-Nuremberg, West Germany, the primarily diagnostic procedure was at the same time a therapeutic one in 226 cases.

These included the electrosurgical removal of polypoid lesions, the extraction of foreign bodies, the removal of nonabsorbable suture material, treatment with injections, electrocoagulation, and partial electroresection of inoperable malignant tumors.

"The removal of polyps with the high-frequency diathermy snare must today be considered the method of choice," Dr. Peter Frühmorgen told the Third International Congress of Gastrointestinal Endoscopy here.

"Compared with the more time-consuming and personnel-intensive surgical method, it represents a less stressful and risky method for the patient. When invasive carcinoma has been excluded by the workup, this primarily diagnostic procedure represents a therapeutic measure, as it also does in the case of bleeding or invaginntion-prone polyps."

222 Polypoid Lesions Removed

A total of 222 polypoid lesions were removed by this method. An open snare that can be turned through about 120° was developed for the removal of larger pedunculated or multilobed polyps. With this instrument, the size and form of the head of the polyp no longer represents a limiting factor for resection, Dr. Frühmorgen said.

He stressed that not biopsy but only complete removal and histologic examination of the polypoid lesion can provide the necessary information on biological nature.

Other procedures carried out by the West German team with the one- or two-channel endoscope were:

- Recovery of a transintestinal tube incarcerated in the upper sigmoid colon, as well as the pellet-filled guide, with the aid of a hook fixed to the tip of a flexible tube introduced through the instrument channel of a colonoscope.
- Removal of nonabsorbable suture material observed to be invading the intestinal lumen of about 10 per cent of all patients examined postoperatively. When a suture could not be removed with the biopsy forceps, it was first divided with the aid of a special high-frequency diathermy probe and then removed with the forceps.
- Sclerosing by injection for the first time of solitary vascular hamartomas in the caecum and transverse colon through the use of an injection cannula located at the tip of a flexible Teflon tube introduced through the instrument channel.

Hitherto, Dr. Frühmorgen said, injections performed with the aid of the endoscope were limited to the local treatment of gastric ulcers or early carcinomas. However, the new procedure was successful only in individual cases, and because of the danger of artificially induced bleeding and the frequent necessity of repeated injection, it was decided to manage these lesions by electrocoagulation.

- Electrocoagulation of hemangiomas with the use of a flexible coagulation probe in a patient with recurrent intestinal hemorrhages of 10 years' standing unsuccessfully treated by injection. The patient has been symptom-free for two years.

A hemangioma in the caecum of another patient was sclerosed during the phase of acute hemorrhage, averting laparotomy.

Nevertheless, because of the danger of perforation the procedure was not considered to have reached the stage of general clinical application.

- Partial electroresection and coagulation of inoperable malignant tumors by use of the high-frequency diathermy snare, a palliative measure, was considered to be of probable utility in the prevention of ileus and in the treatment of bleeding from carcinomas.

Identifying Candidates for Fatal Attack

It is now possible to identify persons most likely to die from a sudden heart attack, according to Dr. Charles Oliver, of Washington University, by using a portable heart-monitoring device and a small IBM computer to pick up premature ventricular contractions usually given off before a sudden and fatal heart attack. Superimposed here is an abnormal heart "blip" identified with arrow and V by computer. Lower tracing shows normal heart beats.

Testosterone Link To Sex Activity Uncertain

By FRANCES GOODNIGHT

Medical Tribune Staff

NEW YORK—A study of 12 heterosexual couples has shown that sexual activity including intercourse does not necessarily produce an increase in the plasma testosterone levels of either man or woman, Dr. Robert C. Kolodny of St. Louis reported here.

Dr. Kolodny, who directs the endocrine research section of the Reproductive Biology Research Foundation, said the study also showed no correlation between the "intensity of the orgasmic experience" as described by either partner and any change in testosterone level.

The first finding differs from observations on animals since coital stimulation causes levels of this hormone to rise in such diverse species as the rabbit, bull, and rhesus monkey, Dr. Kolodny told the annual meeting of the American Association for the Advancement of Science.

Participants in the human study were volunteers—not patients—and did not have any form of sexual dysfunction, the investigator noted. Furthermore, the sexual activity took place in the privacy of the couples' homes. They drew their own blood samples, approximately 30 minutes before the start of sexual activity, immediately prior to coitus, and within one minute following orgasm.

One-third of the men demonstrated a 20 to 50 per cent increase in circulating testosterone levels in association with orgasm "on a very consistent basis," Dr. Kolodny said. Yet at the same point in sexual activity other men showed little change or even a slight decrease in testosterone.

Sexual play, with or without intercourse not leading to orgasm, did not produce significant increases in testosterone levels. Masturbatory activity (self-stimulation or partner-stimulation) that led to orgasm caused only minor increases.

The reported intensity of the orgasmic experience was uncorrelated with change in plasma testosterone, and no clear-cut preceding peak in luteinizing hormone levels was observed before a testosterone rise.

The men showed no consistently seen change in any of the endocrine measures during a week-long abstinence from sexual activity. Dr. Kolodny continued. But findings from a separate study suggest "that longer periods of sexual abstention—combined with anticipation of resuming sexual activity—may produce increases in testosterone levels in men."

Women Less Consistent

The women among the volunteer couples had less consistent increases of circulating testosterone levels in association with orgasm than did the men, Dr. Kolodny said, but those who showed increases did so by much higher percentages.

As with the men, there was no correlation between endocrine change and the reported intensity of orgasmic experience. There was also no association between the phase of the menstrual cycle and the endocrine response to sexual activity of either the male or female partner.

Discussing the possible effects of high and low levels of testosterone, Dr. Kolodny emphasized that "biologic factors are usually secondary in importance to psychosocial ones in human sexual behavior."

He pointed out, however, that androgen is a major biologic determinant of libido. Women who have undergone bilateral adrenalectomy "frequently report diminished interest in sex and decreased sexual responsitivity" and the human male without adequate androgen support "typically reports both a lowered interest in sex and decreased effectiveness in his sexual functioning."

If men with such symptoms have testosterone levels that can be documented as subnormal, he commented, adequate replacement of the hormone will often relieve the problem even though "psychological counseling may be required" to help the patients deal with fears and feelings of inadequacy that developed because of the impotence.

Dr. Kolodny said that studies made at the St. Louis research center of more than 300 impotent men have shown that testosterone levels in impotence are usually normal unless an organic process affecting the endocrine system is present or unless there is drug-induced impotence.

The Only Independent Weekly Medical Newspaper in the U.S.

Medical Tribune
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A Moratorium on Research . . .

AND NOW comes the proposal that society should consider a "moratorium" on the participation of the poor in medical experimentation. This suggestion is a "logical" extension of prior events and points the direction in which they lead.

The proposal was made because the poor are more often the subjects of medical research than the well-to-do. For the same reason, should there be a research moratorium on blacks, chicanos as well as certain ethnic subjects such as Puerto Ricans, who may be more heavily represented among research subjects than is the general population?

Since rigid restrictions and proposals for limiting research have already been put forth to "protect" mentally defective and even normal children, the unborn fetus, the pregnant woman, prisoners and patients in mental institutions, we are well on our way to the ultimate *reductio ad absurdum*—a moratorium on all biomedical research. One must recognize that in fairness to the non-poor, non-black, non-ethnic, non-prisoner, non-fetal, non-pregnant population and to the mentally healthy that they too should not be included in research since they would then be discriminated against and would be represented in research programs disproportionately to their numbers in the diseases investigated.

. . . Victimizes the Sick . . .

BECAUSE the poor and the minority groups have a higher incidence of morbidity and mortality, because the mentally deficient and psychiatric patients are already suffering serious disabilities, the proposed moratorium on research would condemn to a continuation of their disadvantaged and unhappy state the very individuals whom this proposal purports to protect.

Who will suffer by the termination of research on sickle cell anemia—blacks or whites? Who will suffer by the termination of research on mental deficiency, the normal or the mentally retarded? Who will suffer by termination of research on diseases and disorders of pregnancy and of childhood as well if not the pregnant woman and the child?

. . . With No Moratorium on Disease

THERE IS NO moratorium on disease and the disabilities imposed by metabolic and congenital disorders. What is being proposed is actually an insensitive "unilateral disarmament" of man in his age-old fight against disease and its destruction of life. As long as there is no moratorium on disease, there can be no moratorium on research.

A.M.S.

Decision Analysis

LAST YEAR, an article in the *Quarterly Journal of Medicine* discussed "The Application of Decision Theory to the Prevention of Deep Vein Thrombosis Following Myocardial Infarction." The reference is to statistical decision theory, which utilizes formal mathematical calculations of possible consequences in order to develop a decision analysis.

Prevention of deep vein thrombosis was chosen to demonstrate the mathematics utilized to decide whether or not to institute prophylactic heparin therapy following myocardial infarction. The variables involved are the age of the patient, the incidence of deep vein thrombosis in such a patient, how often embolization occurs in the latter circumstances if anticoagulation is begun at that time rather than prophylactically before thrombosis, how often death ensues, and how often anticoagulation itself is hazardous and results in morbidity and death. The incidence of these events varies not only with the age of the patient but whether he has varicose veins, whether he has had a previous thromboembolism, whether he is a smoker—and according to experience of all these events in the particular hospital where he is admitted.

Once the different probabilities are available—as they were made to be in this example—the calculations are fairly straightforward, though tedious, and the decisions relatively easily arrived at. In other instances, more complex calculations may be necessary but, in any event, what was dealt with here was in a Yes-No, or binary format, which is of course red meat to a computer. It seems fairly clear that decision theory will one day be the course that will be followed for treatment, as well as diagnosis, in the hospital once that area has undergone having its clinical experiences stored within a computer's memory.

In 1973, articles in *The American Journal of Medicine* also dealt with decision analysis and clinical judgment. Decision analysis was described as "now finding application in industrial management, economics and government." The current record of decisions in all three of these areas, however, is an unenviable one. Even when computerized and instantly available, the results of decision analysis themselves must be subjected to rigorous criticism on the basis of continuing experience.

"Here comes Rafferty to tell us about his operation again."
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LETTERS TO TRIBUNE

The Coin's Other Side

In my judgment your January 2nd editorial regarding government efforts to control the cost of medical care reflects a "bunker mentality" which is widespread among physicians. It is very true that unwise government intervention can be oppressive and can interfere with quality care, but there is another side of the coin which we tend to ignore. Medical care costs now approximate 100 billion dollars annually (about 8 per cent of the gross national product) and shows every sign of going higher. Furthermore, any physician who has worked on a hospital utilization committee knows that costs can be trimmed in some areas without reducing the quality of care.

The only policy that makes sense is a combination of vigorous efforts to eliminate wasteful medical care practices and firm opposition to any government moves which would interfere with the quality of care. Admittedly it is difficult at times to tell which is which, but we can expect to retain the confidence of our patients and the respect of the government only if we show a balanced concern for care *and* costs.

ROBERT D. GILLETTE, M. D.
Huron, Ohio

Recertification Comment

Re all specialty boards be committed to recertification (MT, Jan. 22), I would like to comment:

A group of physicians appears to have decided that recertification is important for reasons that I am unable to determine. A clinical investigator would not venture into a broad study such as this without prior double-blinded controlled studies to show that the undertaking is of value.

I know of no evidence in any medical journal that shows that recertification will improve the quality of medical care. I do know that it will increase the cost of medical care.

I would feel that a pilot study showing that the quality of medical care would be improved be done prior to the requirement for recertification. Also, I would feel that the Diplomates of the various boards, not the executive committees who are university-based physicians, be polled to determine whether or not they feel that the recertification should be undertaken.

DAVID S. BLOOM, M. D.,
Diplomate, American Board of Internal Medicine; American Board of Gastroenterology
San Rafael, Calif.

Your headline "All Specialty Boards Committed to Recertification", (MT, Jan. 22) is very incorrect.

You shouldn't publish anything like this which appears to be a fact completed. Nothing can be more from the truth.

We are not accepting recertification, and all specialty boards are not committed to it.

I am an Orthopedic Surgeon, and I know that my boards and the Orthopedic Academy has voted down the acceptance of recertification.

I wish you would make a correction report in the headlines on page 1, in your next issue.

IRVING E. MINER, M.D., P. C.
Manhasset, N.Y.

Dr. William A. Larmon, executive secretary of the American Board of Orthopaedic Surgery, Inc., told MT that the Board representative voted affirmatively at the March 29-30, 1973 meeting of the American Board of Medical Specialties "that A.B.M.S. adopt in principle, and urge concurrence of its member boards with the policy that voluntary periodic recertification of medical specialists become an integral part of all national medical specialist certification programs." However, the Board has not as yet, Dr. Larmon said, moved toward implementation of recertification. Dr. Charles Heck, executive director of the American Academy of Orthopaedic Surgeons, noted that the Academy has "voted against mandatory *recertification and recertification by examination at its annual meeting in 1969, but the principle of recertification, provided it is done through continuing education, is quite acceptable."* —*Ed.*

Aneurysm Bypass Reverses Flow in Aorta

Continued from page 1

dynamically in the Center's laboratories, Dr. Absolon said, but last April 24 marked the first time—to the best of his knowledge—that it had been performed successfully in a clinical setting.

Aneurysm Ruptures

Dr. Absolon said the patient had had a type 3 dissecting aneurysm for some time. Months of antihypertensive therapy had failed to control his blood pressure.

"Then," Dr. Absolon said, "the proximal component of the dissection enlarged and finally ruptured. Fluid aspirated from the chest was bloody.

"While this was happening he went into renal shutdown and lost consciousness, probably from interference with the carotid blood circulation," he added. "While he was on dialysis there was probably an extension of the dissection.

"In addition, he also had some coagulopathy," he said.

The situation was "ominous," Dr. Absolon said, and according to a literature search, no patient who had dissected while on dialysis had survived.

Because of the patient's condition, Dr. Absolon and his colleagues were reluctant to put him on a heart lung machine and proceed with a routine excision of the dissection and replacement with a Dacron graft.

"We decided to go ahead with the procedure we had developed hemodynamically in the laboratory," Dr. Absolon said. This involved putting in an axillary iliac graft and measuring the pressure and flow through the graft.

"One rather bothersome thing was that several papers in the literature stated that if you put a graft like this in dogs, this retrograde perfusion of the viscera invariably produces ... tion," he said. "This did not make any sense, however, because our flow and pressure measurements did not indicate such an effect."

The Hospital Center team then connected the subclavian and iliac arteries with 20-inch Dacron grafts inserted bilaterally just outside the patient's rib cage. When both ends of the aneurysm were clamped off, the Dacron grafts took over the circulation and re-routed the blood up through the iliac... to feed the organs of the ab... The aneurysm was then excis...

The normal aorta measures ... cm in diameter, so that ... at 1.5 cm. diameter each wo... vide the same capacity, Dr. A... said in explaining the reasoning ... the bilateral implants. If so... happened to one of the gr... added, the other would provi... security.

"The patient responded well ... operation," Dr. Absolon said; ... rather surprisingly, his blood p... returned to normal without ... tion."

Value in Specific Circumstan...

Dr. Absolon said the patient's medications now are aspirin ... Persantine, for his peripheral va... disease.

Dr. Absolon said he would not ... this procedure as a panacea" f... placement of aortic aneurysm... feels that it has value in specif... cumstances.

This might include patients in w... a bypass is contraindicated, and ... patients on dialysis, or patients ... coagulation defects, he said. "On... solute indication would be in a p... with a graft that had become infe... or a patient who has an empyem... well as a graft, which would ... indicate placement of a second g...

"Other indications might be a t... racic aneurysm in the presence of ... infection, a pseudoaneurysm follo... a trauma, and perhaps some cas... extensive coarctation of the aorta," ... said.

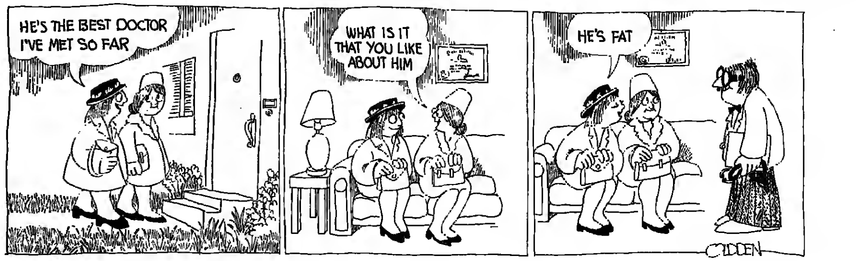
Dr. Absolon's paper on the pro... dure was scheduled for publicatio... the February issue of *Surgery*.

'Most Courageous'

Pittsburgh Steeler running back Rocky Bleier, who was wounded in Vietnam and had two leg operations, with the possibility that he might never again walk normally, was honored by the Philadelphia Sports Writers Association as the Most Courageous Athlete of 1974.

Clinical Trials

by Oldden



Drug Therapy May Remedy An Intracellular Heart Defect

Medical Tribune Report

MARCO ISLAND, FLA.—A strong possibility for a drug therapy to remedy an intracellular defect in diseased heart muscle is emerging from some systematic studies of the molecular activity that occurs when such a muscle cell contracts and relaxes, according to a report here by Arnold Schwartz, Ph.D., Professor of Cell Biophysics at the Baylor College of Medicine.

The key to heart muscle cell contraction and relaxation—the link between the electrical and mechanical processes—is the charged calcium ion, Ca^{++}. At the cell sarcomere, Dr. Schwartz told the American Heart Association's Second Science Writers Forum here, Ca^{++} serves to "open up" a specific site on the actin molecule, which triggers a yet unknown force generating mechanism between the actin and myosin—and causes contraction.

Very Active 'Relaxation'

"Relaxation" of the cell is not what the word implies, Dr. Schwartz said. It is a "very active process" in which the cell's sarcoplasmic reticulum "pulls calcium away" from the site it occupied to trigger contraction. During the heydey of heart transplantation at Baylor, Dr. Schwartz and colleagues minutely examined 35 diseased hearts removed from transplant patients. In all of them, regardless of the causes of the disease, the investigators found a specific defect in the heart cell sarcoplasmic reticulum. The only other common characteristic of the hearts was that they were deficient in pumping ability.

Since then, Dr. Schwartz and associates have been working with dogs in an effort to mimic the failures of the heart muscle cell transport system. Following a lead furnished by Dr. Burton Pressman of the University of Miami, they have been using an experimental antibiotic, RD 2-2985, which is an "ionophore" that has an affinity for such ions as calcium and can move them across membranes.

In dogs pre-treated with the drug and then having coronary artery ligation and induced infarction, the pumping action of the heart is not nearly so decreased as it is in untreated animals, Dr. Schwartz said. If this drug or derivatives of it prove suitably non-toxic, he said, there seems to be a potential for its "extreme value" in warding off cardiogenic shock associated with infarction, and possibly for supporting the diseased heart with chronically flagging contractility.

Hypercholesterolemia

► A drug intervention in the deranged metabolic process associated with familial hypercholesterolemia appears possible from results of an investigation at the University of Texas Southwestern Medical School at Dallas —if the phenomenon seen in human cell cultures can be reproduced in vivo.

Dr. Joseph L. Goldstein, head of the school's Division of Medical Genetics, reported here that the work had disclosed a specific receptor site on the surface of cultured normal fibroblasts that binds low-density lipoproteins, which contain cholesterol in its physiologic form. When cholesterol moves into the cell, it causes a rapid decline in enzyme activity that the cell normally uses for its own biosynthesis of cholesterol and shuts off the intracellular production of it.

But in cells from patients with familial hypercholesterolemia, the binding site for low-density lipoproteins is faulty; the cells continue to produce cholesterol no matter how much of it may be outside.

In an attempt to bypass the faulty site, Dr. Goldstein's group discovered that cholesterol in a non-protein form can gain entry to the cell without depending on the receptor. Once inside, the cholesterol suppresses cell synthesis as it should.

Assuming that cholesterol itself would not be an appropriate therapy for hypercholesterolemic patients, the investigators have come up with several cholesterol analogues—7-ketocholesterol is one—that can get into the cell and specifically suppress cholesterol synthesis, and do it at intracellular concentrations less than a hundredth of that required for cholesterol to produce the same effect.

Transferring the effect from the culture to the whole patient may not be possible with the cholesterol analogues now in use, Dr. Goldstein said, but it seems likely that some analogue can be devised to bypass the faulty lipoprotein site and reverse the syndrome of familial hypercholesterolemia, which he calls "the most common simply inherited disorder in man."

Heterozygotic frequency of the disorder in the general population is about 1 in 500; among survivors of myocardial infarctions the frequency is 1 in 20. Only about one person in a million is homozygous for the disease—is born with a blood cholesterol of 1,000 mg. per 100 ml. and dies of myocardial infarction by age 20.

Egyptian Soldiers in Israeli Hospital Found to Excel in Wound Recovery

Medical Tribune World Service

TEL AVIV—The Egyptian soldier resists infections better than the Israeli, recovers faster from his wounds, and suffers fewer complications, according to a study performed following the Yom Kippur War.

The investigators were physicians at the Sackler School of Medicine of Tel Aviv University and the Assaf Harofuah Hospital, near here. Their conclusions were published in *Harefuah*, the journal of the Israel Medical Association. The study dealt with 372 Israeli soldiers and 118 Egyptian prisoners of war. The two groups were similar in age and received similar treatment for similar wounds from same doctors.

One difference, however, that gives a partial explanation for the findings, the investigators said, was the fact, that the Israeli soldiers had mostly received first-aid treatment shortly after being hit and were hospitalized within six to eight hours, whereas the Egyptians had mostly received no or inadequate first aid and were hospitalized one or two days after being hit.

Thus, the report said the wounded Egyptians who lived long enough to be picked up by their captors, while many of their comrades died, were a selected population exemplifying the principle of the survival of the fittest.

Greek Infant Death Rate

Medical Tribune World Service

ATHENS—The death rate of infants (0-11 months) in Greece is now 30 per thousand as against 38 per thousand 10 years ago, but is still high in comparison to other developed European countries, according to Dr. Christos Kassimos, of Salonica University.

'Roll-Over' Test Flags High BP Of Pregnancy

Continued from page 1

stand around for 15 minutes, they would rather take a blood sample and send it off to the lab, so we wound up with our nurses doing it," Dr. Gant said.

If the diastolic pressure rises more than 20 ml. Hg. above the constant base-line reading, the patient has a 90 per cent chance of developing hypertension, he said.

'Little We Can Do'

"Please don't make me out as a zealot for this screening test," Dr. Gant told a press conference later. "There is little we can do for them except lower their physical activity. If I had a drug to give them, I would demand that every physician give the test, but I don't have a drug." However, he did advocate the test for pregnant teen-agers, who with an incidence of 20 to 25 per cent, represent the highest risk group. It should be done between the 28th and 32nd week, he said.

"If we have beds, we admit such patients for rest; if we have no beds we watch them carefully as outpatients. Many of them get to term and then develop hypertension, while others get to the 36th week and then we deliver them. Those who do not develop the hypertension early on are the ones most at risk."

The hypertension may lead to eclampsia, grand mal seizures, and to severe growth retardation of the fetus, he said. In fact, he added, the fetus should be referred to as the second patient.

Can Modify Eclampsia

"Eclampsia is a chronic disease which develops many weeks before we can measure the changes with a blood pressure cuff. In many patients the changes occur 14 to 16 weeks before the development of hypertension. But if we can detect the disease we can modify it with rest," Dr. Gant said.

Medication to bring the mother's blood pressure down is not appropriate, he said, because the reduced blood flow reduces the functional placental reserve for the baby."

Pasteur Institute in Deep Financial Trouble

BY JAMES MAGEE
Medical Tribune World Service

PARIS—The famed Pasteur Institute, source of medical research that has earned eight Nobel prizes and a world resource in the understanding and treatment of infectious diseases, is in deep financial trouble.

Traditionally 70-80 per cent self-supporting, but with an increasing operating deficit and outmoded and crowded facilities, the Institute faces the need for greatly increased Government financial support; so desperate is the situation, in fact, that it is seriously contemplating selling its present site and moving out of Paris.

In 1973 Institute director Jacques Monod, Sc.D., drew public attention to the difficulties facing the research center, as it headed into its sixth consecutive year of worsening finances.

See One Man and Medicine, pg. 18

"If we are to survive, then we must accept the fact that we have to become more and more dependent on state aid," Henri Perrier, the Institute's principal spokesman, told MEDICAL TRIBUNE here. "At present state help amounts to about 20-30 per cent of our income. If we are to keep going, this assistance will have to be virtually doubled."

In the end it will be Madame Simone Veil, France's tough-minded new Minister of Health, who will decide. But first she has called for information, and the whole Pasteur organization is being reviewed by Government experts. At the same time the scientists and managers on the staff are being interviewed, and their reactions and suggestions recorded for later analysis.

Buildings Dilapidated

But there is more to the problem than the present working deficit. An old print of the inauguration of the Pasteur Institute in 1888 shows women in bustles and gendermes with sabers walking in the grounds of the main building. The sabers have vanished, and the bustles have given way to bottom-hugging blue jeans, but the central buildings remain unaltered by the passage of almost a century.

Grouped tightly around the central campus are a jumble of other buildings of verying architectural styles, from French neo-classic to the glass and steel of the recently-constructed molecular biology wing.

Many of the laborntories built in 1887 are still in use today, and there have been wernings that some of the elder installntions are getting positively dangerous. The gelleries and glazed roof sectiens of the chemistry building are weak, and the maze of ancient piping that brings electricity, gas, and water through the labs has been described as a plumber's nightmare.

This has evidently not affected the work of the Institute, and Dr Monod himself carried out most of his Nobel prizewinning research in an attic. But, as Mr. Perrier point out, there must finally be an end to improvisation If the Pasteur tradition of scientific achievement is to be maintained, the research staff must have buildings and equipment adapted to modern needs. Room must also be found for a projected 20 per cent increase in research staff, particularly in the departments of immunology and virology.

Accordlng to staff consensus, there are only two solutions either to tear down and rebuild on the present site, or pull out of Paris altogether.

Some Want Mediterranean Site

For some of the younger scientists, nostalgic for the academic centers of the U.S. West Coast, this would be a good time to create a French Berkeley or Stanford on the Mediterranean. Why not put the Pasteur Institute down near Antibes, for example, and use it as a magnet to draw other research centers away from the domination of Paris?

But in the eyes of the Institute's governing board, such concepts are *folklore*, a word that for the French has come to signify anything unpractical. Some powerful stalwarts, including Monod's co-Nobelist Dr. Francois Jacob, want to demolish and rebuild on the Paris site. They point out that it is hallowed ground, with Pasteur's apartment and his tomb part of the central building. Furthermore, it is close to all the main Paris hospitals, which facilitates research contacts and training.

Architects retained by the Institute estimate that the work would take at least six years, would cost some 150,-000,000 francs (about $30,000,000), and create huge difficulties in maintaining research activities. Considerations of this kind are already holding up the construction of a new department of immunology, for which the Institute received a donation of 10,000,000 francs from the Rayne Foundation in London in 1971.

Monod Would Rebuild at Garches

Dr. Monod's idea is that the Institute should sell its real estate, which he calculates is worth 220-240,000,-000 francs. He would use 150-160,-000,000 to rebuild at Garches, a location 10 miles outside Paris where the Institute already has some buildings. There would still be enough left over to wipe out the debt burden, calculated to reach around 70,000,000 by 1977.

For some, the idea hints of sacrilege. But Dr. Monod points out that in fact Pasteur died at Garches, and a Pasteur museum could be constructed there. To objections that it is outside the city, he answers that it is only 10 miles away. In any case, the Pasteur vaccination center would remain in Paris, for practical reasons, and could be the nucleus for a Pasteur memorial.

There are still some snags. "We cannot be certain that the Paris City Council will allow rebuilding on the site if we sold it," Mr. Perrier admits. "They might insist on making it parcel space, with the Pasteur house the center. If that was their decision the real estate would fall to a value of only about 60-80,000,000 francs and we would still face major financial difficulties."

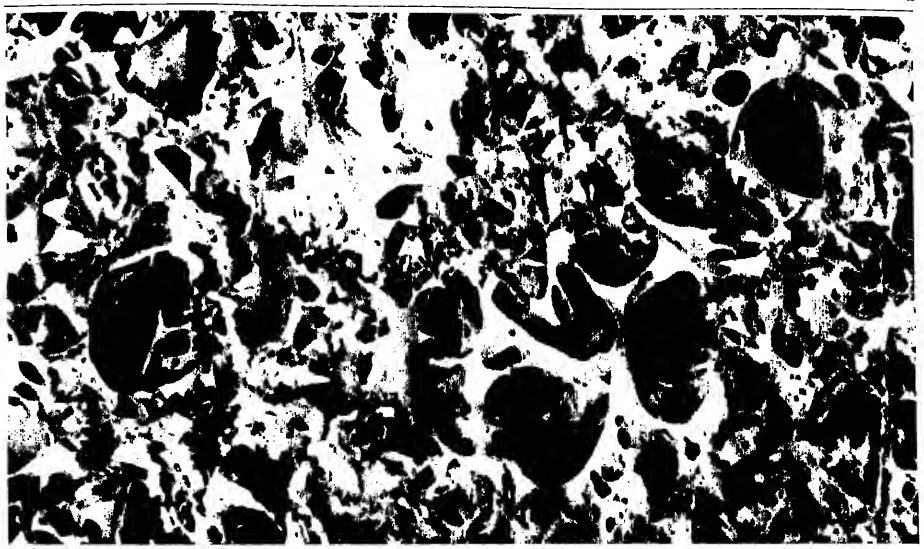
Another drawback is that the land at Garches does not belong to the Institute. It is in fact on loan from the Ministry of Education (an arrangement made with Pasteur in 1888), so official permission might not be forthcoming for construction on the site.

Dr Monod submitted his plan to the governing board of the Institute last October, and although they did not give the green light, they authorized him to give it further study and to seek more information. No one so far has come up with an alternative, short of a huge subsidy from the Government.

Mass fermentation produces a wide range of vaccines, including BCG, cholera, malaria, typhoid, and flu, as well as antitoxins for diphtheria, tetanus, botulism, and staphylococcus.

Pasteur in his laboratory.

Germfree mouse raised at the Institute.

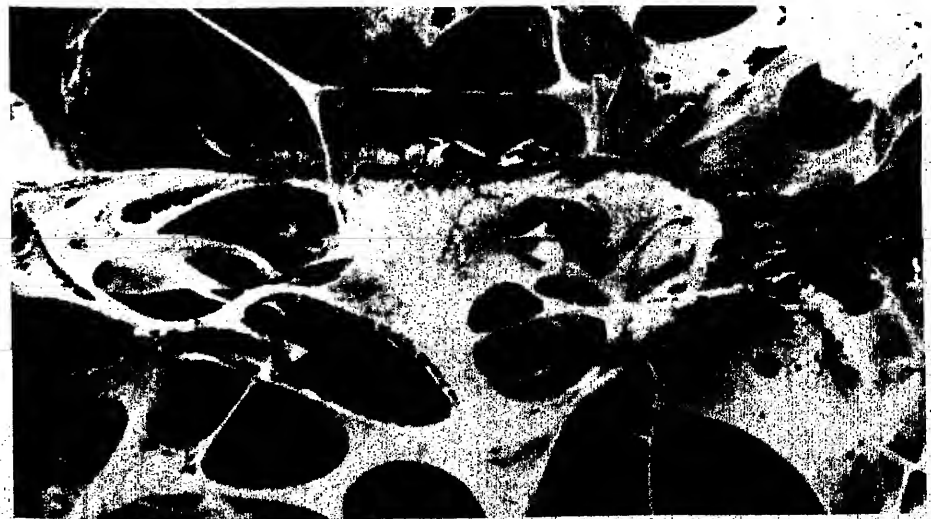


Portion of normal human lung shown by scanning electron microscope.

Emphysema—Fastest Growing Cause of Death

EMPHYSEMA, the most rapidly increasing cause of death in the United States, is now the third leading cause of death from respiratory disease. Emphysema takes many forms. When considered together with chronic bronchitis, the two are referred to as chronic obstructive pulmonary disease. Both emphysema and chronic bronchitis produce breathlessness, cough, and increased susceptibility to respiratory failure and death. Chronic obstructive pulmonary disease attacks middle-aged men and women and is particularly common in smokers. It is now believed that early abnormalities (physiologic and biochemical) related to emphysema and chronic bronchitis may be detected at a stage when lung damage is still reversible.

A new and promising method—measurement of closing volume—has been developed for the early detection of changes in lung function and structure that appear to be the first signs of chronic pulmonary disease. It is presently believed that in persons with abnormal closing volume measurements but with otherwise normal lung function tests, the progression of disease may be reversed and disability prevented with proper treatment and the cessation of smoking.



Human lung with emphysema.

WHO Aide Offers Rapid, Easy Way To Gauge Libido

Medical Tribune World Service

MEXICO CITY—A rapid, uncomplicated method for "measuring" libido as part of the assessment ef systems of fertility regulation was suggested here at the Fourth International Cengress of Hormonal Steroids.

"Until now," said Dr. Patrick Rowe, medical officer, Human Reproduction Unit, World Health Organization, "we hove not found any satisfactory means of accomplishing this necessary task even though scientists in the behavioral field, particularly those in the WHO-sponsored programs in various parts of the world, are developing improved methods, mainly in the form of questionnaires, for evaluating possible changes in sexuality.

"I must admit to a modicum of squeamishness in proposing that eentimeters be the measure for quantifying something like libido, but it might work and I would like to see someone try it."

The system is a direct transposition to libido of one that has already proved successful in assessing depression, the Aitkin Personality Self-Rating Scale, he said.

Cards Marked Daily

The subject is supplied with a batch of cards, each of which hss a line 10 cm. long on it. At one extreme the words, "The Sexiest I Have Ever Felt," appear, and at the other, "The Least Sexy I Have Ever Felt," or the appropriate local equivalent where ths test is being conducted. Each day the person makes n mark on the lino at the point which is considered to correspond to his or her sexnal desire.

The card is then immediately deposited in n box provided for the purpose, and the box eollected at the end of a designated period. The distance along the line to the point where the mark is made is measured and tabulated. The investigator is then able to see over a course of treatment whether there is an upward or downward trend or no change.

"Assessment of libido is, of course, a very tenuous matter," Dr. Rowe commented. "Although theoretical designs for oontrolled studies in the area exist, they provide large scops for the imagination but little practical application. One investigator obtained reports of sharp changes in libido in a group of subjects upon varying the color of the pill being administered. The eard system will eliminate investigator bias and to a large degree the subject's embarrassment, inhibition, or whatever reaction might distort reality.

Greek Aid on Grafts Urged

Medical Tribune World Service

ATHENS—The adoption ef special legislation to facilitate use of cadaveric kidneys was urged here by Dr. Anthony Billis, Associate Professor at Athens University. He said the percentage of kidney transplants using cadaveric donors is only 35 per cent lo Greece and is dropping.

Tribune Economic Analysis

Dollar Anxieties Inhibit Foreign Buying of Stocks

BY ELIOT JANEWAY
Consulting Economist

Foreign buying is the only alternative to a resurgence of popular mass participotion in the stock market. Consequently, the bet that the Dow Industrial average will make it back above 800 is hinging on the calculation that stock prices are olready high enough for the foreigners to jump in and give them an odded whirl for the last mile.

However, one very specific consideration plaguing foreign speculators is new anxiety about the dollar.

Huge Treasury Borrowings

The Europenn foreign exchange markets hove been agog over the dollar inflating the borrowing needs of the U. S. Treasury for the next 18 months. To be sure, Europe is not yet oware that the Treasury's money-raising operation will force it to borrow over $125 billion in the next year and a holf. This is o minimum, subject to continuous inflotion as fast as spending increases and the slump depresses collections.

The sudden, pronounced weakness of the dollar in Europe stands as a warning that foreign buyers may not be quite as ready to rush into New York stocks. Foreign money players dumping the dollar are not likely to accumulnte stocks in Wall Street. Unless they do, 1975's brave new rally will be riding for nnother hard fall.

Do you have any ndvice for those of us small-town fellows who bought mutual funds?

Dr. M. M., Maine

If they're well managed, stick with them and buy more for the long pull. That's the only wny mutual funds ever pay off, and they do for those with the means and the patience to continue accumulnting them on the way down.

The fund managements which pass muster never put on a flashy performance in any year of speculative exuberasce, but were always content te run a comfortable second. If it's any comfort to you, the well managed funds have always continued to grow through bad markets.

Before the end of the year, I have to make a decision about my Keogh funds. I am thinking about a mutual fund. I am in my early fifties and will have about $6,500 te invest. Any advice or suggestions would be appreciated.

G. A., M.D. Louisiana

I think Keogh funds are suitable for investors in your circumstances. However, my suggestion as to selectivity is that you choose income funds whose dividends you can compound rather than funds oriented toward growth and therefore involving speculatien in volatile stocks while limiting income returns.

One Man . . . and Medicine

ARTHUR M. SACKLER, M.D.,
International Publisher, Medical Tribune

The Vicissitudes of the Pasteur Institute

ON MY FIRST TRIP to France in 1949, I made a pilgrimage to the birthplace of Claude Bernard. I was moved to establish it as a shrine to the mind of man, but was too late. In the years that followed, at international congresses and scientific meetings and in personal contacts I've met so many great French scientists that I became a scientific Francophile. Today, it is with deep sadness that one observes the vicissitudes of the organization which commemorates the achievements of another of France's and one of the world's greatest scientists, the Pasteur Institute.

The founding of the Pasteur Institute came upon a wave of public appreciation for a pioneering social and scientific philosophy. For Pasteur, service to industry in the manufacture of wine and vinegar, the salvage of sericulture and aid to farmers to protect their flocks against anthrax and chicken cholera were not simple, menial commercial tasks but scientific levers of opportunity in the contest between the "forces of destruction" and those of "peace, work and health."

Origins of Institute

Pasteur did not derrogate the daily efforts of vintners and farmers whose profits and produce he sought to protect. His dedication to industry and agriculture, rather than impeding, actually aided his penetrating genius to "enlarge the frontiers of life." He opposed the "law of blood and death" which "sacrifices hundreds of thousands of lives to the ambition of a single individual." It was comprehensible, in fact absolutely natural, that the Institute which was to honor his name would rise from blueprints contributed without fee and from the voluntary labor of French workers who gave generously of their time while men and women of all nations made monetary contributions.

Since its founding, following Pasteur's appeal at a meeting of the French National Academy for an independent institute, the Pasteur Institute's activities have exemplified its founder's credo that science should be independent of bureaucracy, governmental or educational, and that there is no dichotomy between basic and pure research but that fundamental medical investigations must be inextricably linked with the practical task of the conquest of disease. As a result, a unique scientific institute evolved on what is now an historic thirteen-acre site in Paris. Here, on the Left Bank, a staff of over 2,000 carry on research at the highest levels, run a hundred-bed hospital and in their laboratories and hundred thousand volume science library give post-graduate training to over 300 fellows from throughout the world. The Institute is much more than a simple memorial to a great scientist, more than a museum housing Pasteur's notebooks, his original laboratory and even his living quarters over it. It is more than a scientific shrine in which a great scientist is entombed in its marble and onyx memorial chapel protected by the mosaic angels—Science, Faith, Hope and Charity.

In the 80 years since Pasteur's death his Institute has been a living presence in biology and medicine, fulfilling his dream of research and service. Pasteur's own research on rabies and anthrax and those of his successors on tuberculosis, diphtheria, yellow fever, tetanus and viruses have been linked to the development of vaccines and sera, to their production and distribution so that since Pasteur's day more and more nations not only in Europe but in Africa as well have been assured that the Pasteur Institute know-how would be available in reliable preparations for the fight against disease.

The Pasteur Institute has been permeated not only by the physical "presence" of its founder and his laboratory but more importantly by his philosophy. That the eminent researchers who are Pasteur's scientific heirs have added most significantly to the Institut's and France's scientific glory is reflected in the Nobel prizes awarded to eight of their members.

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Today, the Pasteur Institute is appropriately headed by a man in Pasteur's own mold—Nobel laureate Jacques Monod, scientist, brilliant philosophic activist, and author. I always find Monod as charming as he is fascinating and a most thoughtful and considerate host. His gentle manner cloaks a probing, ranging mind.

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Jacques Monod forthrightly faces a tragic irony. At a time of epochal achievement and upon the verge of major breakthroughs, the fiscal viability and therefore the independence of the Pasteur Institute is being sapped. It is a bad time. The "guardian angels" of Pasteur's memory can provide little help. Science confronts a growing anti-science. Hope becomes hostage to fear and both Faith and Charity are derrogated by men of little faith and less charity.

The survival of the Pasteur Institute and its rebuilding, its independence from governmental bureaucracy and its continuing ability to put basic sciences at the service of man now rest in the hands of one man. The director of the Institute is, in his genius and intelligence, in his boldness and innovation, in his basic philosophy and his ability to articulate it, a worthy heir to the man who gave his name to what has become a glory of France and of the world of science.

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Medicine on Stamps

Hammurabi

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Text: Dr. Joseph Eh
Stamp: Minkus Publications, Inc., New York

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Medical Tribune World Service

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"The drug approving agencies lag dreadfully behind the practicing physician," he said. "We find drugs being used—and quite properly—for uses not intended at time of initial approval.

"Our system suffers from inability to validate clinical experience of the more usual type—the experience of the clinician weighs so little in the scale. Physicians to be sure are not always right, but they are not always wrong. We should be able to use their clinical experience better than we are now doing."

Dr. Lasagna said the bulk of adverse reactions are not from new drugs, but from older, well established drugs which are not promoted with great zest by the drug industry.

Among problems to be solved, he said, are the questions of how much evidence is enough, who shall judge the evidence, and the need to define safety and efficacy properly.

"We should make better use of foreign data. There is no need to repeat animal experiments, to go on endlessly butchering mice, rabbits, cats and dogs in country after country."

He said a new drug cannot be tested properly, before marketing. "Before marketing it is studied by experts, usually working on homogenous populations, often in-patients, with a minimum of other drugs in the act, and then when the drug is released it is suddenly used by non-experts in a heterogenous population, often in out-patients with other drugs in the act."

He stressed the need to formalize post-marketing surveillance. "If we can guarantee post-marketing surveillance of high quality, then we can argue quite rationally for a speedier approval of drugs." He also argued that drug education is inadequate. "I find that our patients in Rochester are quite interested in getting information on drugs from either the doctor or pharmacist, or from labels or specific inserts for patients."

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Exceptionally well absorbed oral broad spectrum antibiotic may be taken with meals

Larocin™ (amoxicillin) achieves high blood and urine levels

Low incidence of diarrhea to date in clinical studies

NUTLEY, N.J.—Roche Laboratories recently introduced an oral broad spectrum antibiotic: Larocin (amoxicillin). Larocin represents a significant contribution to antibacterial chemotherapy, one which will perform effectively in the treatment of a wide range of infections due to susceptible organisms (see chart at right).

Absorption called the key

The key pharmacological characteristic of Larocin (amoxicillin) is its rapid and efficient absorption from the gastrointestinal tract. Not only is it stable in stomach acid, but the presence of food has no significant effect on the antibiotic's absorption. Thus Larocin may be taken by patients on a convenient *t.i.d.* schedule without regard to meals. The reconstituted oral suspension and pediatric drops may be added to liquids such as formula, milk, fruit juice or soft drinks for easy administration to small children.

Because of its efficient absorption characteristics, high blood and urine levels of Larocin (amoxicillin) are rapidly achieved. Peak serum levels average 4.2 mcg/ml two hours after a single 250-mg oral dose and 7.5 mcg/ml one hour after a single 500-mg oral dose—both levels approximately twice as high as those obtained with equal doses of ampicillin.[1,2]

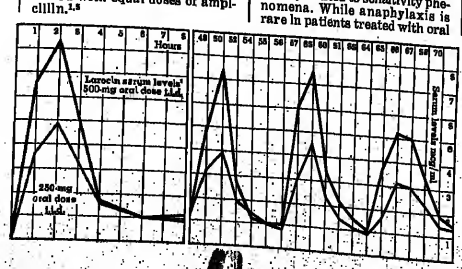
On a multiple-dose regimen, when given every eight hours for 3 days, the lowest mean serum levels of Larocin approximated 1.0 mcg/ml after 250 mg and 1.25 mcg/ml after 500 mg.[2] Although the therapeutic range of blood levels for the penicillins is not well established, these results demonstrate that blood levels may be expected to remain above the MIC's for all of the nonurinary pathogens susceptible to Larocin when it is administered at clinically recommended doses (see chart below).

Most of Larocin is excreted unchanged in the urine.[3] Average urinary excretion within 6 to 8 hours after oral administration ranges from 40 to 79% for the 250-mg dose and 59 to 79% for the 500-mg dose.[1-4]

I. Croydon EAJ, Sutherland R: *Antimicrob Agents Chemother*—1970, pp. 427-430, 1971. 2. Neu HC, Winshell EH: *Antimicrob Agents Chemother*—1970, pp. 428-436, 1971. 3. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey. 4. Leigh DA: *Curr Med Res Opin* 1:10-18, 1972. 5. Bodey GP, Nance J: *Antimicrob Agents Chemother* 1:358-362,1972.

Hypersensitivity reactions can occur

As with other penicillins, it is anticipated that adverse reactions to Larocin (amoxicillin) will be largely limited to sensitivity phenomena. While anaphylaxis is rare in patients treated with oral penicillins, the possibility must nevertheless be kept in mind. Larocin is contraindicated in patients with a history of penicillin hypersensitivity. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT (See Warnings section of complete product information, a summary of which appears at right.)



GRAM-POSITIVE	
Alpha-hemolytic streptococci Beta-hemolytic streptococci *Streptococcus faecalis*	
Diplococcus pneumoniae	
Nonpenicillinase-producing staphylococci	
GRAM-NEGATIVE	
Hemophilus influenzae	
Escherichia coli	
Proteus mirabilis	
Neisseria gonorrhoeae	

In vitro bactericidal activity

Note: Because Larocin (amoxicillin) does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria such as resistant staphylococci. All strains of Pseudomonas and most strains of Klebsiella and Enterobacter are resistant.

Efficacy demonstrated in many infections

Amoxicillin has been administered successfully to patients with a wide range of commonly seen infections due to susceptible organisms.* Over-all clinical evaluation of amoxicillin therapy was considered a "success" or "improvement" in 1267 of 1850 evaluable cases (93.3%).†

Ages of the 1850 patients studied ranged from under one year to over 80 years. Larocin capsules were administered to 800 patients and oral suspension to the remaining 550. Dosage of the capsules ranged from 250 mg *t.i.d.* (the most frequently used dosage) to a single 3-Gm dose for the treatment of acute uncomplicated gonorrhea. Dosage of the oral suspension ranged from 50 mg *t.i.d.* to 250 mg *t.i.d.*, with 125 mg *t.i.d.* the most frequent. The majority of patients were treated from seven to 10 days. A breakdown by type of infection follows:

Otitis Media: The pathogens most commonly isolated were *Diplococcus pneumoniae* and *Hemophilus influenzae*. Of 130 cases with this diagnosis, 122 (93.8%) were rated as a "success" or "improvement" after treatment with Larocin (amoxicillin).

• • •

Streptococcal Sore Throat: A success rate of 86% (174 of 202 cases) was observed with Larocin against the responsible pathogen, beta-hemolytic streptococci.[5] The great majority of the 202 patients in this group were children who received the oral suspension.

• • •

Other Upper Respiratory Infections: Beta-hemolytic streptococci were the offending organisms for most of the infections in this group, which were diagnosed primarily as pharyngitis, with some cases of tonsillitis and a few cases of sinusitis. A success rate of 82% (56 of 68 cases) was achieved with Larocin.

• • •

Lower Respiratory Infections: Treatment with Larocin resulted in "success" or "improvement" in all of the 52 cases in which *Diplococcus pneumoniae* was cultured. *Staphylococcus aureus* was also cultured in 26 of the 28 cases; Larocin showed "success" or "improvement" in 96% (25 of 26 cases). The most common clinical conditions were bronchitis and bronchopneumonia.

• • •

Urinary Tract Infections: Cystitis, pyelonephritis and asymptomatic bacteriuria were the most frequent clinical diagnoses in this group. Of the 404 cases evaluated, *Escherichia coli* was cultured in 306 cases and treatment with Larocin resulted in "success" or "improvement" in 284 cases (93%). *Proteus mirabilis* was cultured in 70 patients, with Larocin effective in 67 (96%).

• • •

Skin and Soft Tissue Infections: *Staphylococcus aureus* was cultured in 108 cases, with "success" or "improvement" in 104 (96%); while beta-hemolytic streptococci were cultured in 99 cases, with "success" in 97 (98%). Impetigo and abscess were the most frequent diagnoses.

• • •

Gonorrhea: Administered as a single 3-Gm oral dose, Larocin showed a success rate of 97% in both males (85 of 88 cases) and females (114 of 118 cases).

**Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.*
†"Success" or "improvement" was determined by a combination of clinical and bacteriological criteria. In infections due to beta-hemolytic streptococci and N. gonorrhoeae, only successes were included.

Low incidence of side effects reported to date

During the clinical investigations with amoxicillin, all cases treated were evaluated for side effects. No side effects or laboratory abnormalities which would be considered unusual for a penicillin derivative were reported by any of the investigators.

In 2658 total courses of therapy with amoxicillin, therapy was discontinued in only 52 patients (1.9%) because of drug-related side effects. Laboratory abnormalities possibly related to amoxicillin occurred infrequently.

In these studies, there was a low incidence of diarrhea reported with amoxicillin capsules—1.7% or 30 of 1811 patients. Especially noteworthy was this low incidence of diarrhea reported with amoxicillin oral suspension—only 2.8% or 24 of 847 patients, significantly less ($p<0.05$) than the incidence of diarrhea with ampicillin oral suspension (5.8% or 15 of 282 patients).

In breaking down the over-all incidence of diarrhea by age groups, it was found that in the group from 0 to 1 (newborn and 1-year-old infants), 13 of 108 patients receiving amoxicillin oral suspension developed diarrhea, for an incidence of 12%. This represents over one-half the total number of diarrhea cases seen in the 847 patients treated with amoxicillin oral suspension.

Throughout each of the remaining age categories, starting from age 2 to 10 and in the general grouping from age 11 to 20, the incidence of diarrhea in patients treated with amoxicillin oral suspension ranges from 2% down to 0 in the older groups. There were few cases of diarrhea beyond the age of six.

The incidence of diarrhea with Larocin (amoxicillin) can therefore be expected to be considerably higher in the newborn and infant age groups than in older children, which is true of all antibiotics.

Drug-Related Side Effects Associated with Amoxicillin

Based upon 2658 courses of therapy: 1811 with the capsules and 847 with the oral suspension.

SIDE EFFECT	CAPSULES #	CAPSULES %	SUSPENSION #	SUSPENSION %
Diarrhea	24	1.3	18	2.1
Rash	24	1.3	17	2.0
Nausea	7	0.3	1	0.1
Urticaria	8	0.4	2	0.2
Moniliasis	7	0.3		
Nausea/Vomiting	4	0.2		
Diarrhea/Nausea	3	0.1		
Vomiting	2	0.1	4	0.4
Dizziness	2	0.1		
Colitis	2	0.1		
Nausea/Headache	2	0.1		
Rash/Urticaria	2	0.1	1	0.1
Esophageal Spasm	1	0.05		
Stomachache	1	0.05	1	0.1
Belching	1	0.05		
Drowsiness	1	0.05		
Belching/ Numbness/ Tingling/ Itching	1	0.05		
Fever/Itching	1	0.05		
Difficult Breathing	1	0.05		
Mucus in Pharynx	1	0.05		
Diarrhea/Urticaria	1	0.05		
Diarrhea/Vomiting	1	0.05	4	0.4
Dizziness/Headache	1	0.05		
Conjunctival Ecchymosis	1	0.05		
G.I. Bleeding	1	0.05		
Abdominal Cramps	1	0.05		
Diarrhea/Rash	1	0.05	1	0.1
Rash/Diarrhea/Vomiting			1	0.1
Sore Tongue			1	0.1
Rash/Vomiting			1	0.1
TOTAL	102	5.8	82	6.1

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Infections due to susceptible strains of the following gram-negative organisms: *H. influenzae, E. coli, P. mirabilis* and *N. gonorrhoeae*; and gram-positive organisms: streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinase-producing staphylococci. Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine causative organisms and susceptibility to amoxicillin.

Contraindications: In individuals with history of allergic reaction to penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH MORE FREQUENT FOLLOWING PARENTERAL THERAPY, ANAPHYLAXIS HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. MORE LIKELY IN INDIVIDUALS WITH HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE THERAPY, INQUIRE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF ALLERGIC REACTION OCCURS, INSTITUTE APPROPRIATE THERAPY AND CONSIDER DISCONTINUANCE OF AMOXICILLIN. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. ADMINISTER OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, AS INDICATED.

Usage in Pregnancy: Safety in pregnancy not established.

Precautions: As with any potent drug, assess renal, hepatic and hematopoietic function periodically during prolonged therapy. Keep in mind possibility of superinfections with mycotic or bacterial pathogens; if they occur, discontinue drug and/or institute appropriate therapy.

Adverse Reactions: As with other penicillins, untoward reactions will likely be essentially limited to sensitivity phenomena and more likely occur in individuals previously demonstrating penicillin hypersensitivity and those with history of allergy, asthma, hay fever or urticaria. Adverse reactions reported as associated with use of penicillins: ***Gastrointestinal:*** Nausea, vomiting, diarrhea. ***Hypersensitivity Reactions:*** Erythematous maculopapular rashes, urticaria. ***NOTE:*** Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Discontinue amoxicillin unless condition is believed to be life-threatening and amenable only to amoxicillin therapy. ***Liver:*** Moderate rise in SGOT noted, but significance unknown. ***Hemic and Lymphatic Systems:*** Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, agranulocytosis. All are usually reversible on discontinuation of therapy and believed to be hypersensitivity phenomena.

Dosage: ***Ear, nose, throat, genitourinary tract, skin and soft tissue infections***—Adults: 250 mg every 8 hours. Children: 20 mg/kg/day in divided doses every 8 hours; under 6 kg, 0.5 ml of Pediatric Drops every 8 hours; 6-8 kg, 1 ml of Pediatric Drops every 8 hours. ***Lower respiratory tract infections and severe infections or those caused by less susceptible organisms***—Adults: 500 mg every 8 hours. Children: 40 mg/kg/day in divided doses every 8 hours; under 6 kg, 1 ml of Pediatric Drops every 8 hours; 6-8 kg, 2 ml of Pediatric Drops every 8 hours. ***Gonorrhea*** (acute uncomplicated anogenital and urethral infections)—Males and females: 3 grams as a single oral dose. NOTE: Children weighing more than 8 kg should receive appropriate dose of oral suspension 125 mg or 250 mg/5 ml. Children weighing 20 kg or more should be dosed according to adult recommendations.

Note: In gonorrhea with suspected lesion of syphilis, perform dark-field examinations before amoxicillin therapy and monthly serological tests for at least four months. In chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller than recommended doses should not be used. In stubborn infections, several weeks' therapy may be required. Except for gonorrhea, continue treatment for a minimum of 48-72 hours after patient is asymptomatic or bacterial eradication is evidenced. Treat hemolytic streptococcal infections for at least 10 days to prevent acute rheumatic fever or glomerulonephritis.

Supplied: Amoxicillin as the trihydrate: Capsules, 250 mg and 500 mg; oral suspension, 125 mg/5 ml and 250 mg/5 ml; pediatric drops, 50 mg/ml.

Usual Adult and Pediatric Dosages

INDICATION	STRAIN ISOLATED	ADULT DOSAGE	PEDIATRIC DOSAGE*
Infections of the ear, nose, throat	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, *H. influenzae*	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Infections of the lower respiratory tract	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, *H. influenzae*	500 mg t.i.d.	Oral Suspension: 40 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 1 ml t.i.d.; 6-8 kg (13-18 lbs): 2 ml t.i.d.
Infections of the genitourinary tract	*E. coli*, Proteus mirabilis, Strep. faecalis	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Infections of the skin and soft tissues	Streptococci, susceptible staphylococci and *E. coli*	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Severe infections, or infections caused by less susceptible organisms		500 mg t.i.d.	Oral Suspension: 40 mg/kg/day in divided doses t.i.d.
Gonorrhea, acute uncomplicated anogenital and urethral infections (males and females)	*N. gonorrhoeae*	3 grams—single oral dose	

*Note: Children weighing more than 8 kg (18 lbs) should receive the appropriate dose of the Oral Suspension: 125 mg or 250 mg/5 ml. Children weighing more than 20 kg should be dosed according to adult recommendations.

'Doctors Often to Blame'

Timely Action Urged in Tay-Sachs Pregnancy

BY MICHAEL HERRINO
Medical Tribune Staff

BROOKLYN—"Doctors are often to blame when Tay-Sachs disease is not detected by amniocentesis between the 16th and 22nd weeks of a woman's pregnancy, in time for therapeutic abortion if necessary," Dr. Bruno Volk, director of the Isaac Albert Research Institute of Kingsbrook Jewish Medical Center and Clinical Professor of Pathology, State University of New York, Downstate Medical Center, told MEDICAL TRIBUNE.

Adequate screening of persons of child-bearing age for Tay-Sachs carriers is presently the only way to prevent this incurable, autosomal recessive disease, he said, but it is wholly preventable if doctors are aware of the importance of early prenatal diagnosis.

A Sphingolipidosis Ward

Kingsbrook is still conducting mass screening programs of college students at risk and members of various Jewish organizations in the New York metropolitan area, running the world's only maintenance ward for patients with sphingolipidosis, and continuing its basic research in enzyme-deficiency diseases, despite severe losses in financial support, Dr. Volk reported.

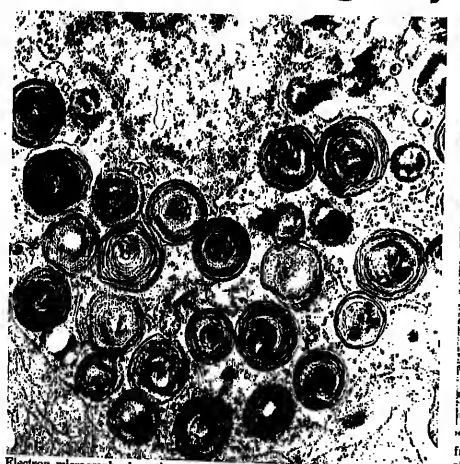
"We lost support from N.I.H. during the Johnson Administration, and this year the Tay-Sachs Foundation has cut its grant by 60 per cent. So we've felt the pinch as badly as everybody else," he said.

Although a "cure" of Tay-Sachs is a long way off in his opinion, Dr. Volk said that a good possibility for it may lie in experiments such as those underway at Kingsbrook with purified hexosaminidase A (Hex A). Lack of this isoenzyme in the amniotic fluid and cells aspirated from the fetus by amniocentesis is a sign that it has Tay-Sachs disease and should cause the parents to strongly consider a therapeutic abortion, he stated. "In some of our experiments, fetal nerve tissue from these abortions was used to see if the missing enzyme Hex A can enter the cells and thereby prevent Tay-Sachs."

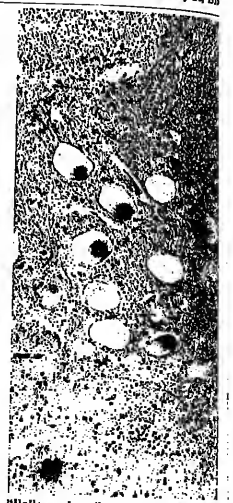
Animal Models Studied

In the event that this proves feasible, he added, investigators at Kingsbrook are also studying animal models that may be the counterpart of the gangliosidosis of Tay-Sachs in man, to determine whether replacement of a missing enzyme (not necessarily Hex A) can prevent the disease. "Tay-Sachs in man is caused by the neuronal degeneration of the central nervous system because of progressive intracellular accumulations of excessive amounts of the sphingolipid known as ganglioside G_{M2}. So far we believe that our animal models have a G_{M1} gangliosidosis, a relative of the G_{M2} gangliosidosis in Tay-Sachs, so we don't know how far to extrapolate these findings to the human situation," Dr. Volk said.

"The most important phase of our research to date is still mass screening. The patients of highest risk are Jewish couples when both individuals are of Eastern European origin. If both of these prove to be Tay-Sachs carriers, one child in four could be born with the disease.



Electron micrograph of portion of "ballooned-out" neuron, showing deposited ganglioside in the form of concentric membranous bodies. Lack of isoenzyme hexosaminidase A results in the accumulation.



"Ballooned-out" ganglial cells of the frontal lobe of Tay-Sachs infant show effect of excess amounts of ganglioside G_{M2}. Gradual accumulation of ganglioside eventually leads to neuronal degeneration of C.N.S.

"With amniocentesis, we can accurately predict which one of those four is afflicted before it is born. We can also help the woman who has already endured the experience of a previous Tay-Sachs baby and may be suffering severe anxiety that she will have another. When we assure these women that they can have a healthy baby without fear, the relief for them is sometimes unbelievable.

"The birth of a Tay-Sachs child can traumatize an entire family for life," Dr. Volk said. "In addition to the nightmarish experience of watching a healthy-looking infant slowly turn into a vegetable and 'black out,' the expense of caring for a Tay-Sachs patient is a financial sacrifice of the first order—as much as $50,000 a year for the constant care required. So even though the overall risk may be small, Tay-Sachs is an overwhelming burden when it occurs. And the chances of this are 100 times as great for Ashkenazi Jews than other Jewish and non-Jewish populations," Dr. Volk explained.

Glycolipids Not Metabolized

"We've already learned that in Tay-Sachs, certain glycolipids are not metabolized due to the lack of Hex A. These substances accumulate in the gangliocytes, causing them to 'balloon out' and produce within three to five years psychomotor degeneration characteristic of the disease," he said.

"As many as one out of every 30 Ashkenazi Jews in the United States may be heterozygous for the defect," Kingsbrook, he pointed out, has been active in securing legislation in the city council to see that a pamphlet on Tay-Sachs is available at all marriage license bureaus in the city.

The real responsibility for early detection, Dr. Volk maintained, is on all practicing physicians.

"Until we find a cure, mass screening of high-risk sectors of the population and midtrimester amniocentesis of suspected pregnancies, are the only means we have of dealing with Tay-Sachs, and the only hope for learning more about it," Dr. Volk concluded.

"The explosion of knowledge about the sphingolipidoses in the past ten years has meant remarkable progress in identifying the genetic factors involved.

"With continuing educational programs and publications, we hope to increase medical understanding and awareness of Tay-Sachs disease. I think this is essential to our overall success."

Kingsbrook's special 16-bed ward is said to be only maintenance ward for patients with Tay-Sachs and other sphingolipidoses in the world.

16-OH Steroids in Low-Renin Hypertension

Medical Tribune World Service

MEXICO CITY—A significant role for the 16-hydroxylated compounds in low-renin essential hypertension was suggested here by two teams of U.S. investigators at the Fourth International Congress on Hormonal Steroids.

One group found what was described by Dr. James Melby, Professor of Medicine at Boston University, as a "unique steroid structure and a unique steroid effect." This compound, reported for the first time, was identified by Dr. Sidney L. Dale as 16 alpha, 18-dihydroxy-DOC. Conversion of labeled 18-OH-DOC to the new structure was shown to be greatly accelerated by the adrenal tissue in patients with low-renin essential hypertension. It was found to be secreted in superabundance in this condition.

"Twenty per cent of all hypertensive patients in the United States have low plasma-renin activity," Dr. Melby said, "and findings in them are remarkably similar to those in patients with primary aldosteronism. Knowing, however, that only 1 to 2 per cent actually have primary aldosteronism, we looked for a different steroid structure."

Steroid Antagonists Suggested

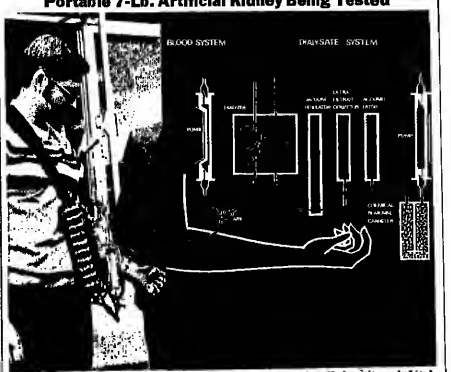
Four such patients showed excess 16 alpha, 18-dihydroxy-DOC—which made the investigators think that it could be important in the genesis of suppressed renin in a certain proportion of patients with hypertension because of the unique activity of this steroid, which appears to function as a cooperative or positive allosteric effector of aldosterone. This was thought to be one of the first demonstrations of such an effect.

Clinically, the interpretation of the finding was that in a significant percentage of patients having normal steroid secretion, treatment would be more specific with use of steroid antagonists.

Another new 16-hydroxylated steroid, also excreted in excess in patients with low-renin essential hypertension, unexplained activity was purified and was identified by mass spectral analysis as 16 beta-hydroxydehydroepiandrosterone (16 beta-OH-DHEA). That this steroid is in fact a mineralocorticoid was confirmed by demonstrating that synthetic 16 beta-OH-DHEA has a sodium-retaining capacity one-40th that of aldosterone.

Dr. Liddle found 24-hour urinary excretion of the new mineralocorticoid to be above the normal range in 15 patients with low-renin essential hypertension and in no patients with hypertension who had normally responsive plasma-renin activity. The interpretation of this phenomenon was that 16 beta-OH-DHEA could be a cause of low-renin essential hypertension.

Portable 7-Lb. Artificial Kidney Being Tested



A portable 7-pound artificial kidney is being tested by University of Utah scientists. A patient on this kidney undergoes two hours of dialysis daily. This maintains an even chemical balance in the blood and prevents a waste-produce buildup. The patient must also spend one hour with the unit hooked to a 20-L. tank for the removal of urea.

Corticosteroid Prophylaxis Aids Prematures

Medical Tribune World Service

BERLIN—Corticosteroid management during the 32nd week of pregnancy or later has been found to reduce the incidence of hyaline membrane disease considerably in premature infants, Dr. H. Eckert, of Frankfurt University Women's Clinic, told the Seventh Germany Perinatal Medicine Congress here.

One significant observation, the investigator said, was that corticosteroids specifically bring about an increase in surfactant phospholipid content.

The prophylactic effect of corticosteroids relative to lung maturity in premature infants is more significant for hyaline membrane disease morbidity than mortality, Dr. Eckert said.

In all single births born in the 18 months prior to adoption of cortisone prophylaxis at the Frankfurt clinic, the incidence of hyaline membrane disease was classified retrospectively as a function of gestational age and weight at birth.

Before the thirty-second week of pregnancy, incidence was 64 per cent; during the thirty-second to thirty-sixth weeks inclusive 30 per cent; and after the thirty-sixth week only 0.5 per cent.

Corticosteroid prophylaxis for pregnant women with premature pangs during the latter half of pregnancy, Dr. Eckert said, consists of intravenous administration of 60 mg. 16-methylprednisolone on each of at least three consecutive days. Prior to therapy, amniocentesis is performed to determine the stage of development.

Significant Rise in Lecithin

Dr. Eckert's group has obtained lecithin and creatinine charts and clinical analyses of fetuses after corticosteroid prophylaxis in 42 pregnant women compared with 30 unmanaged controls.

While creatinine did not react appreciably with 16-methylprednisolone stimulation, there was a significant rise in lecithin as a determinant surfactant parameter after three days of corticosteroid management, the investigator said. The more advanced the pregnancy the more pronounced this rise in lecithin level became. Before the thirty-second week of pregnancy none was observed, from the thirty-second through thirty-sixth weeks it came to 40 per cent and after that to 56 per cent. No rise in lecithin was recorded in the unmanaged controls.

The stimulant effect of corticosteroid on lecithin synthesis was confirmed by animal tests both in vivo and in vitro.

Dr. Eckert described 26 premature births delivered after corticosteroid prophylaxis during the thirty-first through thirty-seventh weeks of pregnancy. The mothers had been given 60 mg. 16-methylprednisolone at least 24 hours and not more than seven days before the delivery. Three prematures, two of them before the thirty-second week of pregnancy, developed a typical membrane syndrome despite prophylaxis; in three other prematures a previously unobserved form of the membrane syndrome was noted, which was distinguished clinically by its short and comparatively mild course, though exhibiting typical pO_2 and pCO_2 alteration. These modified, fairly mild forms seemed generally more frequent after corticosteroid management, Dr. Eckert said.

IMMATERIA MEDICA

The Western Slope

● Dr. Harold Zimmerman of Laramie, Wyo., was taken by the ending of a piece in *Cutis:*

"When the older physician saw this patient, he made the diagnosis within seconds; the younger physicians were completely ignorant of both Dr. Meleney or the cause for the ulceration. *'Sic gloria transit.'"*

He feels the Latin is putting the cart before the hearse. We figure Gloria was sick but had to travel.

● "In comparing a six month duty tour of mainland China during 1945 to a recent one-month visit in 1973 is about as parallelistic as an overladen cesspool is to a Palm Springs condominium."

—*Utah Medical Bulletin*

Some of those Palm Springs condominiums are getting awfully parallelistic, we understand.

Once again: contributions to Immateria Medica are welcome. Send in the best anecdote you heard at a meeting.

Good fluid balance.
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In the group of 16 prematures delivered between the thirty-second and thirty-sixth week of pregnancy, the incidence of hyaline membrane disease amounted to five per cent; one child developed a severe membrane syndrome in conjunction with sepsis, which eventually proved lethal.

Incidence 30% in Controls

One other child, delivered at a weight of 1300 grams during the thirty-third week of pregnancy, survived with a modified form of hyaline membrane disease. In the control group without management, adjusted to age, the incidence of hyaline membrane disease was 30 per cent.

Coauthors were R. Gerner, E. Halberstädt and V. Loewenich.